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Citation

Boffetta, Paolo, Vijayvel Jayaprakash, Ping Yang, Kofi Asomaning, Joshua E. Muscat, Ann G. Schwartz, Zuo-Feng Zhang, et al. 2010. Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case-control studies in the International Lung Cancer Consortium (ILCCO). *Cancer Causes & Control* 22(1): 73-79.

Published Version

doi:10.1007/s10552-010-9676-5

Permanent link

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Tobacco smoking as a risk factor of bronchioloalveolar carcinoma of the lung: pooled analysis of seven case–control studies in the International Lung Cancer Consortium (ILCCO)

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Received: 9 April 2010 / Accepted: 18 October 2010 / Published online: 12 November 2010
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Abstract

Background The International Lung Cancer Consortium (ILCCO) was established in 2004, based on the collaboration of research groups leading large molecular epidemiology studies of lung cancer that are ongoing or have been recently completed. This framework offered the opportunity to investigate the role of tobacco smoking in the development of bronchioloalveolar carcinoma (BAC), a rare form of lung cancer.

Methods Our pooled data comprised seven case–control studies from the United States, with detailed information on tobacco smoking and histology, which contributed 799

cases of BAC and 15,859 controls. We estimated the odds ratio of BAC for tobacco smoking, using never smokers as a referent category, after adjustment for age, sex, race, and study center.

Results The odds ratio of BAC for ever smoking was 2.47 (95% confidence interval [CI] 2.08, 2.93); the risk increased linearly with duration, amount, and cumulative cigarette smoking and persisted long after smoking cessation. The proportion of BAC cases attributable to smoking was 0.47 (95% CI 0.39, 0.54).

Conclusions This analysis provides a precise estimate of the risk of BAC for tobacco smoking.

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Keywords Lung cancer · Bronchioloalveolar carcinoma · Tobacco smoking

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Introduction

Tobacco smoking is the most important cause of lung cancer, being responsible for an estimated 80–90% of cases in most populations of the world [1]. The carcinogenic effect of tobacco smoking on different histological types has been investigated in several studies, which typically included the most frequent types: a stronger risk has been repeatedly reported for squamous cell carcinoma and small cell carcinoma than for adenocarcinoma [2], while the risk of large cell carcinoma, which has been investigated less frequently, seems intermediate [3]. Data on other, rarer histological types are sparse and often based on a small series of cases leading to imprecise risk estimates.

Bronchioloalveolar carcinoma (BAC) of the lung is a form of adenocarcinoma characterized by growth of neoplastic cells along the alveolar structures with limited invasion of the blood vessels, the stroma, or the pleura. A mucinous and a non-mucinous variants are distinguished, the latter being more frequent. Distinction between BAC and other forms of lung adenocarcinoma is often difficult, and cancers, in particular those of larger size, frequently display mixed histologies [4]. BAC is considered a relatively infrequent form of lung cancer, but population-based data on incidence are scant. In the United States, age-adjusted incidence rates in the 1970s and 1980s were between 1 and 2 per 100,000, with little differences between sexes and races [5]. Reviews of series of patients from single institutions suggested an increase in the proportion of BAC over total lung cancers [6, 7], but the limited data from population-based cancer registries support the lack of a trend in incidence [5, 8]. Specific features of the epidemiology of BAC include a comparable incidence in men and women (in several series the number of female cases outnumber that of male cases), a shift in the distribution toward early-stage lesions, and a better survival rates than for other histological types of lung cancer, which is not fully explained by differences in stage at diagnosis [9].

The rarity of this histological type complicates the analysis of its risk factors. A lower proportion of smokers among BAC cases when compared to other types of lung cancer has been reported in early studies [9–12], but only two epidemiological studies have provided a formal estimate of the risk of BAC among smokers relative to non-smokers. In a study of 87 cases from several US hospitals, Morabia and Wynder [13, 14] reported an odds ratio (OR) of BAC for current smoking of 3.9 (95% confidence interval 1.8, 8.7), an increase in OR for increasing duration and amount of smoking, and a protective effect of quitting. In a study of 21 cases from Louisiana, Falk and colleagues [5] reported an OR of 4.0 (95% CI 0.9, 18.8) for ever smoking. Other risk factors have not been adequately investigated.

Pooled analyses within a consortium of data collected in independently conducted studies represent a cost effective approach in generating a large series of cases and controls. We have therefore conducted a pooled analysis of tobacco smoking and risk of BAC within the framework of the International Lung Cancer Consortium (ILCCO), which includes completed and ongoing studies of molecular and genetic epidemiology of lung cancer [15], with the aim of providing a precise measurement of the association between tobacco smoking and BAC.

Methods

This pooled analysis comprises data from seven case-control studies from the United States (Table 1). These studies represent a subset of studies included in the ILCCO collaboration (<http://ilcco.iarc.fr>). The remaining studies participating in the ILCCO consortium either excluded by design rare histological types of lung cancer or enrolled less than 10 BAC cases. The seven studies included one study each from the University of California at Los Angeles (UCLA) [16], Harvard University (HU) [17], University of Hawaii (UH) [18], two studies from Wayne

Table 1 Characteristics of studies included in the pooled analysis of lung bronchioloalveolar carcinoma and tobacco smoking

Study, location	Study design	Definition of ever smoker (cigarettes)	Response rate (%) in ca/co	Total number of lung cancer cases	Number of BAC cases	Number of controls	Special features
UCLA, Los Angeles [16]	Population-based	>100	39/79	611	39	1,040	
HU, Boston [17]	Hospital-based	>100	85/55	2,253	204	1,529	
UH, Honolulu [18]	Population-based	>185	64/62	635	38	588	
WSU1, Detroit [19]	Population-based	≥100	55/71	526	50	460	Women
WSU2, Detroit [20, 21]	Population-based	≥100	66/93	1,006	35	1,184	EO
Mayo [22]	Hospital-based	≥100	87/84	5,698	280	2,269	
AHF [23, 24]	Hospital-based	≥100	92/93	5,130	153	4,942	

BAC bronchioloalveolar carcinoma, *ca* cases, *co* controls, *EO* early-onset cases

State University (WSU) [19–21], one study from Mayo Clinic (Mayo) [22], and one multicentric study coordinated by the American Health Foundation (AHF) [23, 24]. Results on tobacco smoking and BAC risk have been reported for part of the AHF study [13, 14]. For some of the studies, the number of subjects included in the pooled analysis was larger than that reported in previous publication because recruitment has continued. Three studies [17, 22, 23] was hospital-based, and the other four were community-based case–control studies. In the UCLA study, newly diagnosed cases were identified using the rapid ascertainment system of the Cancer Surveillance Program for Los Angeles County. All BAC cases were diagnosed pathologically and validated through pathologic records. A similar approach was followed in the WSU studies, based on the Metropolitan Detroit Cancer Surveillance System. In the HU study, cases were enrolled from the Massachusetts General Hospital in Boston, MA, as part of an ongoing case–control molecular epidemiology study of lung cancer. Pathology reports generated by two pulmonary pathologists as part of routine tissue diagnosis were obtained from the clinical information system. The histological confirmed diagnosis of BAC from pathological reports was reviewed by a study pathologist or oncologist. In the UH study, pathology records were obtained from SEER registries; BAC diagnoses were not validated. In the Mayo study, the histological diagnoses were validated. In the AHF study, information on histology was abstracted from the records of the pathology departments of the participating hospitals and was not validated. The proportion of BAC over total lung cancers varied from 3 to 9%. Information on stage of BAC cases was not available.

All studies collected information on lifetime history of tobacco smoking, including age of start smoking, duration, intensity, and time since quitting for the former smokers. All studies collected information on cigarette smoking; in the UCLA, Harvard, and Hawaii studies, cigar and pipe smoking was added to cigarette smoking to calculate cumulative tobacco consumption. For the purposes of the pooled analysis, we generated common variables related to smoking status (never, ever, current, and former smoker, defined as smokers who have quit more than 1 year before diagnosis or interview), daily amount of smoking (1–9, 10–19, 20–29, 30–39, and 40 or more cigarettes/day), duration of smoking (1–9, 10–19, 20–29, 30–39, and 40 or more years), and cumulative smoking (1–9, 10–19, 20–29, 30–39, and 40 or more pack years, one pack year being equivalent to 20 cigarettes/day smoked during 1 year). Former smokers were further categorized according to time since quitting (1–9 years, 10–19, 20 or more years).

Other variables included in the pooled analysis were sex, age at diagnosis or interview (categorized as up to 50, 51–60, 61–70, and more than 70), education (basic or

elementary, up to high school, and college or more), study center, and race (Asian, Black, White, Hawaiian, Hispanic, other).

All analyses were performed using the STATA statistical package [25]. Study-specific OR of lung cancer and their 95% CI for smoking intensity, duration, cumulative smoking, and time since quitting were estimated using unconditional logistic regression. All the estimates were adjusted for age at diagnosis, sex, race and study center.

We explored the heterogeneity between study-specific results using the Q statistic at the significance level of $p < 0.05$. Galbraith plot where the ratio of the log odds ratio to the standard error (the Z statistic) for each study is plotted against the reciprocal of the standard error [26]. Further, the influence of each study on the overall meta-analysis estimate was analyzed by an influence analysis, where the meta-analysis estimates are computed after omitting each study. Pooled OR estimates stratified by sex, age at diagnosis, education level, and study design were also calculated.

Linear trends for the amount, duration, cumulative smoking, and time since quitting were tested according to Greenland and Longnecker [27], using the ‘*gls*’ command on STATA, which utilizes the generalized least squares for trend estimation of summarized dose–response data. Population attributable fractions were calculated using ‘*aflogit*’ on STATA, which estimates the adjusted measures of population attributable fraction from a logistic regression model [28].

Results

Overall, 799 cases of BAC and 15,859 controls were included in the pooled analysis. Their demographic characteristics are summarized in Table 2. A total of 514 cases (64.3%) and 5,779 controls (48.1%) were women. The median age of cases was 65 years (interquartile range 56–73 years) and that of controls was 56 years (interquartile range: 45–65 years). Table 3 reports the results of the analysis of tobacco smoking. The OR for ever smoking was 2.47 (95% CI 2.08, 2.93); it was 2.51 (95% CI 2.09, 3.01) for current smoking and 2.35 (95% CI 1.90, 2.92) for former smoking. The study-specific ORs for ever smoking are presented in Fig. 1: they ranged from 1.12 in the UCLA study to 3.90 in the AHF study; the p -value of the test for between-study heterogeneity in OR was 0.01. The summary estimate of OR for BAC based on a meta-analysis fixed effects model was 2.38 (2.00, 2.85); the summary OR based on a random-effects model was 2.20 (95% CI 1.51, 3.20). A linear trend was observed for amount of smoking (OR for an increase in 10 cigarettes/day 1.32, 95% CI 1.27, 1.38; p -value of test for between-study heterogeneity 0.07),

Table 2 Demographic characteristics of lung bronchioloalveolar carcinoma cases and controls included in the pooled analysis

Characteristic	Cases		Controls	
	<i>n</i>	%	<i>n</i>	%
Sex				
Men	285	35.7	6,233	51.9
Women	514	64.3	5,779	48.1
Age				
<50 years	95	11.9	3,015	25.1
51–60 years	158	19.8	3,114	25.9
61–70 years	281	35.2	3,606	30.0
>70 years	265	33.2	2,277	19.0
Ethnicity				
White	697	87.6	10,144	84.5
Black	35	4.4	1,002	8.3
Asian	32	4.1	341	2.8
Other	29	3.9	521	4.4
Education				
Lower than high school	60	8.1	900	7.8
High school	308	41.5	5,004	43.6
College or higher	374	50.4	5,563	48.6

duration of smoking (OR for a 10-year increase 1.25, 95% CI 1.20, 1.30; between-study heterogeneity *p*-value 0.01), and cumulative smoking (OR for an increase in 10 pack years 1.29, 95% CI 1.24, 1.34).

Table 4 presents the pooled results for ever smoking stratified by sex, age at diagnosis, and education level. No heterogeneity was suggested with respect to age sex or education level. The proportion of BAC attributable to ever smoking tobacco was 0.47 (95% CI 0.39, 0.54). It was 0.74 (95% CI 0.17, 0.66) in men and 0.37 (95% CI 0.24, 0.48) in women.

Discussion

Our analysis adds strong evidence to the notion that BAC is a form of lung cancer associated with tobacco smoking. The current analysis also provides strong evidence on a beneficial effect of quitting tobacco smoking, as it has been shown for lung cancer in general and for the major histological types [29].

Our results are quantitatively consistent with those of the two epidemiological studies of BAC available in the literature [5, 13, 14]: a meta-analysis of the results for current smoking for the three studies resulted in a *p*-value for heterogeneity of 0.7.

We acknowledge several limitations to our study. We were not able to perform a systematic pathology review of

Table 3 Odds ratio of bronchioloalveolar carcinoma for tobacco smoking in the pooled analysis

	Cases		Controls		OR	95% CI
	<i>n</i>	%	<i>n</i>	%		
Smoking status*						
Ever smokers	600	75.1	7,229	60.3	2.47	2.08, 2.93
Current smokers	180	22.5	2,718	22.7	2.51	2.09, 3.01
Former smokers	415	51.9	4,431	36.9	2.35	1.90, 2.92
Amount of smoking*						
1–9 cpd	71	9.0	1,139	9.6	1.57	1.18, 2.08
10–19 cpd	115	14.5	1,717	14.5	1.93	1.51, 2.46
20–29 cpd	208	26.2	2,213	18.7	2.93	2.38, 3.61
30–40 cpd	85	10.7	898	7.6	3.15	2.39, 4.14
40+ cpd	115	14.5	1,110	9.4	3.79	2.94, 4.90
<i>p</i> -value for linear trend					<0.001	
Duration of smoking*						
1–9 years	33	4.3	865	7.4	0.96	1.53, 1.75
10–19 years	82	10.7	1,241	10.6	1.98	1.30, 3.03
20–29 years	106	13.8	1,623	13.8	1.83	1.23, 2.71
30–40 years	157	20.5	1,618	13.8	2.87	2.10, 3.94
40+ years	189	24.7	1,631	13.9	2.89	2.66, 3.55
<i>p</i> -value for linear trend					<0.001	
Cumulative smoking*						
1–9 pack years	70	9.1	1,606	13.6	1.26	0.95, 1.67
10–19 pack years	74	9.6	1,195	10.1	1.89	1.43, 2.50
20–29 pack years	90	11.7	1,055	8.9	2.60	1.99, 3.38
30–40 pack years	85	11.0	982	8.3	2.81	2.14, 3.68
40+ pack years	254	32.9	2,195	18.6	3.48	2.84, 4.26
<i>p</i> -value for linear trend					<0.001	
Time since quitting**						
1–9 years	87	11.3	1,046	8.8	1.12	0.90, 1.53
10–19 years	138	17.9	1,367	11.5	1.06	0.82, 1.46
20–29 years	84	10.9	1,041	8.8	0.89	0.70, 1.14
30+ years	84	10.9	910	7.7	0.83	0.63, 1.04
Never smokers	199	25.8	4,763	40.2	0.42	0.34, 0.52
<i>p</i> -value for linear trend					<0.001	

CI confidence interval, *cpd*, cigarettes per day, *n* number, OR odds ratio, adjusted for age, gender, race, and study center

* Reference category: never smokers (199 cases, 4,763 controls)

** Reference category: current smokers (180 cases, 2,718 controls)

the cases, and the possibility of misdiagnosis remains open for some cases. However, misclassification is most likely to occur with other forms of adenocarcinoma [4], a type of lung cancer that is less strongly associated with tobacco smoking than other types, and diagnoses of well-differentiated lung cancer have been found to be reproducible [30, 31]. The proportion of BAC over total lung cancer cases varied from over 9% in the HU and WSU1 studies to 3% in the AHF study. A validation of BAC diagnosis was

Fig. 1 Study-specific odds ratios (and 95% confidence intervals) of lung bronchioloalveolar carcinoma for ever tobacco smoking. The combined odds ratio is based on a random-effects model meta-analysis

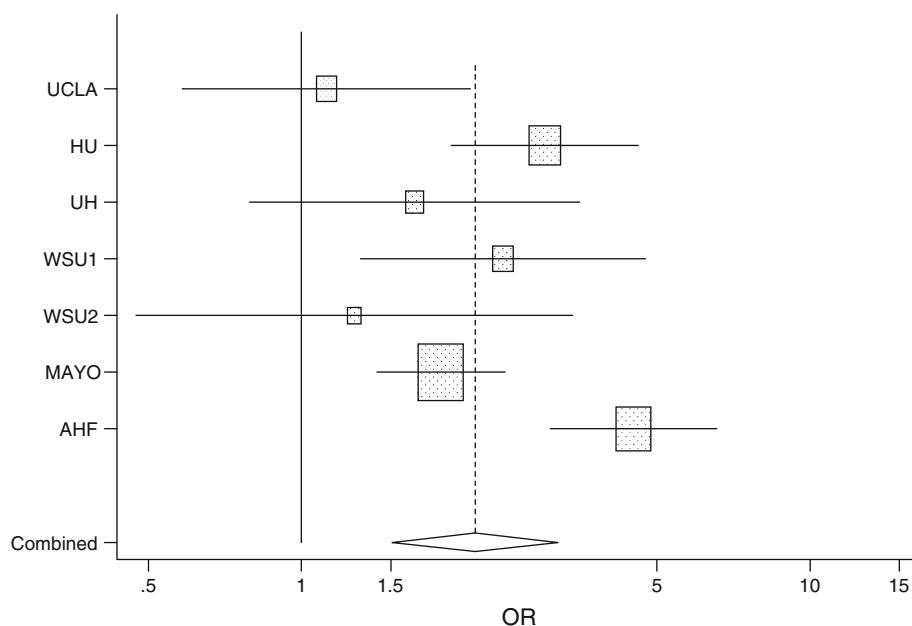


Table 4 Odds ratio of bronchioloalveolar carcinoma for ever tobacco smoking in the pooled analysis, stratified by sex, age at diagnosis, and education

Stratum	OR	95% CI
Sex		
Men	2.10	1.61, 2.91
Women	2.52	2.01, 3.08
Test for heterogeneity, <i>p</i> -value	0.87	
Age		
≤60 years	1.48	0.97, 2.26
50–60 years	2.65	1.78, 3.95
60–70 years	2.39	1.77, 3.23
>70 years	2.73	1.99, 3.70
Test for heterogeneity, <i>p</i> -value	0.12	
Education		
Lower than college	3.05	2.35, 3.98
College or higher	2.39	1.88, 3.05
Test for heterogeneity, <i>p</i> -value	0.18	

CI confidence interval, OR odds ratio, adjusted for age, gender, race, and study center

performed only in some of studies included in this pooled analysis; however, the study-specific results presented in Fig. 1 do not suggest an important role for diagnostic misclassification, since the magnitude of the excess risk did not appear to correlate with validation of pathological diagnosis.

The lack of histological verification also pre-empted us from distinguishing between the two main types of BAC, namely mucinous and non-mucinous. This is unfortunate because the molecular alterations seem to differ between

the two types, with a higher proportion of codon 12 KRAS mutations in the mucinous type and, conversely, a higher proportion of TP53 mutations in the non-mucinous type [32–35]. The high proportion of EGFR mutations in BAC, when compared to other types of lung adenocarcinoma [36], is consistent with a comparatively lesser etiologic role of tobacco smoking in the former type of neoplasm.

An additional potential limitation, which is common to retrospective epidemiological studies, is recall bias, i.e., lung cancer cases over-reporting tobacco smoking when compared to controls, either because of better recall or because they are trying to explain their disease. However, the internal consistency of our results (dose–response relation with amount and duration of smoking, effect of long-term quitting, lack of heterogeneity by sex, age, or education) argues against a strong role of recall bias.

The main strength of our study lies in its size, as it included more than seven times the total number of BAC cases included in previous epidemiological studies on the effect of tobacco smoking on this form of lung cancer. The high quality of participating studies and the validity of the information on exposure and outcome are confirmed by the consistency of inter-study risk estimates.

No results have been reported on risk of BAC after cessation of smoking. The available evidence points toward a more rapid decrease in risk with increasing time since cessation for squamous cell carcinoma than for adenocarcinoma [29]. The similarities between BAC and adenocarcinoma might explain the relatively weak effect of quitting we observed in our analysis.

In conclusion, our pooled study resulted in a twofold increased risk of lung BAC in ever smokers when compared to never smokers, and in evidence of a dose–response

relation according to duration and amount of smoking. Forty-seven percent of BAC cases in the study population would be attributable to the habit. This is the most precise estimate of the risk of BAC for tobacco smoking available in the literature and supports the notion of an association between tobacco smoking.

Acknowledgments The original studies were supported by the following grants: WSU1 and WSU2 studies: NIH R01CA60691, R01CA87895, N01PC35145, and P30CA22453; HU study: NIH R01CA074386, R01CA092824, and P20CA090578; UCLA study: NIH R01DA11386 and R01CA90833; UH study: NIH R01CA55874; Mayo study: NIH-CA 77118, NIH-CA 80127, and NIH-CA 84354; AHF study: NIH CA-32617, CA-68384, CA-29580, and CA-17613.

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